



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels,
F2/SM D (2008)

QUESTIONS and ANSWERS

The rules governing medicinal products in the European Union
VOLUME 2
NOTICE TO APPLICANTS
Volume 2B
Presentation and content of the dossier
Common Technical Document (CTD)
2003 Edition

UPDATE Feb 2008

Common Technical Document (CTD)

Questions and answers

Feb 2008

General Notes

In case of Regulatory or Administrative questions on the NTA-CTD format, specifically concerning EU related procedures, please send an E-mail to entr-pharmaceuticals@ec.europa.eu.

Other questions on the location of studies within the Quality, Non-clinical and Clinical modules or on general CTD related issues should be sent via the IFPMA website: <http://www.ich.org>. Questions related to specific scientific requirements are not covered by these mechanisms.

The question and answers No 1, 5, 10, 11 and 15 have been deleted because these questions dealt with transitional periods which already ended.

The questions and answers No 17a and 17b have been deleted due to the existing guideline on the processing of renewals in the Centralised Procedure and the Mutual Recognition Procedure (<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2c>).

Question 1: deleted

Question 2:

Reformatting of dossiers for already authorised products

After 1 July 2003, is it necessary to reformat the old EU-format (NTA, Volume 2B, 1998) documentation of already authorised medicinal products into the new EU-CTD-format (NTA, Volume 2B, 2001)?

Answer:

NO, there is no obligation to reformat the dossier of already authorised medicinal products into the new EU-CTD format.

If a marketing authorisation holder (MAH) wishes to reformat the documentation, such reformatting will be allowed, although it is not recommended for the Non-clinical and Clinical parts of the documentation. However, for the Quality part of the documentation, companies are encouraged to voluntarily reformat into the CTD-format, especially to facilitate the handling of variations and line extensions after 1 July 2003. Such reformatting must however involve the complete Quality parts, including any DMFs (if applicable) and also including and integrating all approved variations. A signed declaration from the MAH, must also be submitted stating that the content/data of the Quality Module is identical to the currently approved Quality part and that there has been no changes to the dossier as a result of the reformatting.

Re-formatted Quality documentation submitted in the CTD-format must consist of a new Module 3 in CTD format, but need not necessarily contain the Quality Overall Summary together with the signed template for the Quality Expert.

A Module 1 need not be submitted. If the original Part II contained data on bioequivalence, then this data should be extracted from the Part II and reformatted into the new CTD structure, and annexed in a separate binder as a separate section 5.3.1.2.

Any reformatted documentation should also be submitted in electronic format (e-CTD preferred) if available.

The submission of reformatted documentation should preferably occur simultaneously (but separately) with the submission of a variation, line-extension or renewal. As the case may, a clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation / line extension or renewal should be made.

Question 3:

Reformatting – fees?

Is the reformatting of a dossier considered as a variation? Does it attract a fee?

Answer:

Reformatting of a dossier does not fall under the legal definition of a variation, because there is no amendment of the dossier's content.

For dossiers of products which are already approved via Mutual Recognition Procedure in more than one Member State, any reformatting has to be made simultaneously in all the Member States concerned. Where products are approved via national procedures in different Member States it is also highly recommended to reformat the dossiers at the same time.

The relevant competent authority has to decide whether a fee would be charged or not.

Question 4:

Variations

Is it possible to submit a variation application in the new EU-CTD format without reformatting the original dossier which was submitted in the "old" EU format?

Answer:

After 1 July 2003, all variation applications must be submitted using the EU-CTD format. However, cross-references to "old" EU-format documentation will be accepted, because the content is identical. Clear references to any "old" format documentations are essential.

Examples:

Any new (either additional or revised) data in support of the variation must be submitted using the CTD format.

If any data need to be submitted which are unchanged, for example, the Type IA/IB Variation Guideline might specify the need for submission of a copy of the approved specifications, then the marketing authorisation holder should update the specifications into the new CTD-format. The marketing authorisation holder must also provide a declaration that the content of any reformatted documents is unchanged. Any future variation applications would then be able to use these "updated" (CTD) specifications.

Where only a cross-reference to already authorised data is required, such cross-references can still be made to the relevant "old" format dossier (Part and section). However, if the marketing authorisation holder prefers to take the opportunity to present the (unchanged) data in the new CTD-format instead, this would be equally acceptable as it would facilitate the handling of future variations. The marketing authorisation holder must also provide a declaration stating that the content of any **reformatted documents is unchanged**. The submission of reformatted documentation should preferably occur simultaneously (but separately) with the submission of a variation. As the case may be, a clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation should be made.

Question 4a:

CTD-format for Variations:

As since 1 July 2003, all variation applications must be submitted using the EU-CTD format, can you specify the content of Module 1 and 2 for Type II variations?

Answer:

It is suggested to present the documentation for variation applications as follows:

Module 1:

1.0 Cover Letter

1.1 Comprehensive table of content

1.2 Variation Application Form

1.3 Product Information

1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet – where appropriate

1.4 Information about the experts:

The relevant expert declaration(s) and signature(s) must be provided, corresponding to the Overview/Summary submitted in Module 2.

In cases where MAHs wish to distinguish this declaration from any previous declarations, the Variation Procedure Number of the RMS/EMEA may be included on top.

1.5 Specific Requirements for Different Types of Applications

1.5.3 Justification of the newness of the therapeutic indication

In case the applicant wants to claim a one-year data exclusivity at the time of the application for the concerned new therapeutic indication, a document, justifying that the application concerns “a new therapeutic indication” and that significant preclinical and clinical studies have been carried out, has to be provided.

Related study reports and supporting literature references shall be placed in the relevant Modules of the dossier and thus cross-referred to accordingly.

Module 2:

As mentioned in the Variation Regulation, any Type II variation should be accompanied by the relevant Overviews/Summaries updates or addenda (even if a variation is submitted at the request of the Competent Authority). Expert details and signature are to be provided in Module 1.4 separated from the actual Overview/Summary.

Supportive data are to be included in Modules 3, 4 and/or 5 as appropriate and in accordance with the EU-CTD structure.

Documentations for Type IA/IB-Notifications also have to follow CTD-structure, where applicable.

Question 4b:

MRP and Repeat use procedure - CTD-format:

Is it necessary to reformat the dossier before a MRP or repeat use procedure is started?

Answer:

When starting an MRP and repeat use procedure it is an obligation to submit Module 1, 2 and 3 (original submission and following variation) in the CTD-structure. Overviews and summaries of non-clinical and clinical data in Module 2 can be replaced by expert statements with reference to the corresponding expert reports in the “old” EU format, which should be attached.

There is no need to reformat non-clinical and clinical data. It should be stated that Part III corresponds to Module 4 and Part IV to Module 5.

This applies also for **duplicate applications** in MRP and pure national procedures.

Question 4c:

CTD-format for Variations:

How should Type IA/IB notifications be organised to be compliant with CTD structure?

Answer:

In order to comply with CTD structure documents should be organised as follows :

Where a cover letter is provided it should be placed in Module 1, 1.0 Cover Letter.

The checklist of conditions to be fulfilled and documentation to be supplied, i.e. the extract of the relevant page from the Guideline on Dossier Requirements for Type IA and Type IB notifications, should be placed in 1.2 Application Form after the Application Form itself.

Documents should be assigned, wherever possible, to the relevant CTD section, primarily within Module 3 Quality and 1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet. These would include replacement sections and additional information.

Where documents cannot be assigned to specific CTD-defined locations then they should be included in 1.2 Application Form. These might include declarations, certificates, justifications etc. Where possible, they should be organised according to the Annexes for the Application Form for new products (Annexes 1 to 22). Where documents cannot be assigned to one of the annexes then it is appropriate to place them after the annexes. The 'Additional Data' section of Module 1 should not be used except for country-specific information defined in Table 3.2 of Chapter 7, General Information, of the Notice to Applicants.

Documents should be presented with tab dividers for paper submissions or as separate files according to eCTD guidances.

Question 5: deleted

Question 6

Extensions

After 1 July 2003, is it necessary to submit an extension as a complete CTD Application? What should be done with the already authorised Non-clinical and Clinical documentation?

Answer:

After 1 July 2003, all applications for extensions must also be submitted using the new EU-CTD format. However, references can be made to already assessed and authorised "old" Parts of the dossier, but only if no new additional data are submitted in these parts. In such cases, it is not necessary to reformat already assessed and authorised "old" documentation.

Modules 1 and 2 always have to be provided. Where no new clinical and/or non-clinical data are submitted the respective overviews/summaries can be replaced by expert-statements. It is however necessary to provide new CTD-format summaries and overviews to cover any new information or data provided in support of the application. In these CTD-format summaries/overviews, all the headings (numbers and titles) must be included, but where cross-references can be made, as the data has not changed, it is sufficient to include a statement such as "Not changed" (or similar). Marketing authorisation holders are also encouraged, in addition to presenting the new line-extension quality data in the CTD-format, to reformat the entire assessed and authorised "old" format Part II into the new CTD-format, in order to obtain a complete CTD Module 3, covering all strengths/pharmaceutical forms. However it is acknowledged that this may not always be feasible or necessary.

For example in those cases where there are multiple strengths and/or pharmaceutical forms, the Quality module of the line-extension may include only the data for the new strength/pharmaceutical form and cross-refer to the relevant "old" quality data. At the occasion of the next variation affecting the "old" part, marketing authorisation holders should "reformat" (at least) that part into the CTD format.

Question 7:

Generic and hybrid applications

For applications according to Article 10(1) of Directive 2001/83/EC (so called "generic applications"), and for applications according to Article 10(3) of Directive 2001/83/EC (so called "hybrid applications") is it acceptable to submit the dossier as follows: a CTD Module 3 for the Quality data with references to the old format for both the Non-clinical and Clinical data in the originator's product dossier?

Answer:

Yes, that would be acceptable. In addition to Module 3, Module 1 and 2 always have to be provided (see also question 8).

In case bioequivalence data are submitted, a separate section 5.3.1.2 needs to be provided (see answer to question 2).

For "hybrid applications", the relevant data have to be provided in the relevant Modules.

Question 8:

Generic and hybrid applications

For applications according to Article 10(1) of Directive 2001/83/EC (so called "generic applications") and for applications according to Article 10(3) of Directive 2001/83/EC (so called "hybrid applications"), what should Module 2 contain?

Answer:

For applications according to Article 10(1) and (3) of Directive 2001/83/EC, Module 2 must include :

- Quality Overall Summary
- Non-clinical Overview
- Clinical Overview

Non-clinical and Clinical Summaries can be provided, but they are only mandatory if new additional studies have been provided within the documentation.

The written summary of the bioequivalence has to be part of the Clinical Overview.

Question 9:

Herbal medicinal products and traditional herbal medicinal products

Do new applications for herbal medicinal products have to follow the EU-CTD-format? What about traditional herbal medicinal products?

Answer:

Herbal medicinal products follow the rules applicable to medicinal products in general and CTD format is to be followed.

In relation to traditional herbal medicinal products, in October 2007, the Committee on Herbal Medicinal Products has issued a Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products which addresses some specificity of these applications.

Question 10: deleted

Question 11: deleted

Question 12:

Certificates of Suitability

How should information relating to the Drug substance be included within the EU-CTD format when a Certificate of Suitability is available?

Answer:

The Drug Substance section should refer to the Certificate of Suitability in the relevant sections in Module 3.2.S. The Certificates of Suitability are deemed to replace the data of the corresponding sections and therefore in principle no further additional information is necessary except concerning technical characteristics of the substance where not covered by the Certificate of Suitability (e.g. when the Certificate of Suitability does not describe a specific technical grade, information and data for the re-test period).

A complete copy of the Certificates of Suitability (including any annexes) should be provided in the annex 6.10 of the application form in Module 1 and in Module 3 R.

Question 13:

Bibliographical applications

For applications submitted according to Article 10a of Directive 2001/83/EC (well established use), is it necessary to tabulate all the results found in the literature in the clinical and non-clinical summaries of Module 2?

Answer:

According to Article 10a of Directive 2001/83/EC, it is possible to replace results of pharmacological and toxicological tests or clinical trials by detailed references to published scientific literature (information available in the public domain), if it can be demonstrated that the constituent(s) of the medicinal product has a well established medicinal use, with recognised efficacy and an acceptable level of safety.

For such applications, the provisions of the Annex I to Directive 2001/83/EC shall apply in like manner. They are considered as full and independent applications.

Clinical and non-clinical summaries in Module 2 shall be provided. Summaries may not be necessary for very old, well known substances, but a proper justification will be required.

Overviews always have to be provided.

Question 14:

Active Substance Master File (ASMF)

How should the relevant information on the Drug Substance be submitted in the CTD format when an ASMF is used for new applications?

Answer:

The applicant's ("open") part of the ASMF should be included in section 3.2.S of the Quality documentation presented in the CTD-format.

The current EU guideline on the ASMF procedure applies, i.e., it is the responsibility of the applicant for a marketing authorisation for a medicinal product to ensure that the complete ASMF, that is both the applicant's ("open") part and the active substance manufacturer's restricted ("closed") part is supplied to the authorities directly by the active substance manufacturer in the CTD format, synchronised to arrive at around the same time as the marketing authorisation application. A copy of the "Letter of Access" shall be included in Annex 6.10 of the application form, in Module 1 and addressed to the regulatory authority to where the application is made.

The active substance manufacturer's restricted ("closed") part of the ASMF should follow the structure of Module 3.2.S of the CTD. A separate Quality Overall Summary for the information included in the active substance manufacturer's restricted ("closed") part should also be provided, as part of the ASMF.

After 1 May 2005 (end of the second transitional phase for ASMFs), any ASMF referred to by a new application needs to be completely presented in the CTD format (open and closed part and the Quality Overall Summary on the ASMF), regardless of the procedure followed (i.e. centralised, mutual recognition/decentralised or national).

Question 15: deleted

Question 16:

**Changes to the Active Substance Master Files (ASMFs) - variations
After July 2003, how should changes to the ASMF be formatted?**

Answer:

If a change concerns a section of an ASMF, the documentation for this change must be submitted in the CTD-format. The ASMF-holder should be strongly encouraged to reformat the complete ASMF at this occasion. This will facilitate the handling of changes/variations which affect data in the ASMF concerned.

The ASMF-holder should make a clear distinction between the reformatting of the ASMF-data, already assessed by the competent authorities and the new documentation supporting the change to ASMF-data.

If an ASMF is reformatted into the new EU-CTD-format without any change in data, a signed declaration must be provided by the ASMF-holder certifying that the content of that ASMF is identical to the currently held version of the ASMF.

After reformatting of the ASMF, the new “open part” of the ASMF in CTD-format has to be sent by the ASMF-holder to the MAHs concerned, in order that the MAH is able to update all marketing authorisations where that ASMF has been used. It will be acceptable to have the ASMF in the CTD format, without reformatting of the corresponding Quality data in the dossier of the medicinal product.

If there is a change to the ASMF-data, the corresponding variation has to be submitted to the authorities by the MAH. For general guidance on variations – see Q&A No. 4.

For extension applications to MAs where an ASMF is used, the ASMF Holder should reformat the complete ASMF into the EU-CTD-format so that the “new” format ASMF can be included in the line extension application, rather than any cross reference being made to an “old” format ASMF.

Question 17 a: deleted

Question 17 b: deleted

Question 18:

When submitting Follow-up Measures, a Specific Obligation dossier or a dossier including post-marketing experience, does the CTD structure need to be used?

Answer:

The CTD structure should always be utilised whereby documents are assigned to the most appropriate sections in Modules 1-5. They should be structured according to the granularity defined in the ICH guidance on CTD Organisation, Annex: Granularity Document (CPMP/ICH/2887/99 Rev 2 Correction Organisation CTD) with Tables of Content and tab dividers for paper submissions or as separate files according to eCTD guidance.

When submitting via the Centralised Procedure the Post-authorisation Guidance provided on the EMEA website (<http://www.emea.europa.eu/htms/human/postguidance/index.htm>) should also be considered.

Question 19:

PSUR:

When submitting a Periodic Safety Update Report (PSUR) as a stand-alone document or as part of a broader submission such as a Renewal, where should it be placed within the CTD structure?

Answer:

The PSUR should be located in Module 5.3.6, Reports of Post-Marketing Experience. If a Summary Bridging Report is also to be provided then this should be included in Module 5.3.6 as well.

Question 20

Module 1.3.5

Which information has to be put in Module 1.3.5?

Answer:

In section 1.3.5 “Product Information” all the relevant documentation concerning the Product Information has to be provided.

Among others Article 8(3)(1) of Directive 2001/83/EC states that copies of the Summary of Product Characteristics and the Package Leaflet approved by competent authorities of the Member States in accordance with Article 21 and Article 61 have to be provided.

Therefore, for applications in a Mutual Recognition Procedure copies of the approved Product Information of the relevant medicinal product, as approved by Member States, need to be provided in Module 1.3.5.

This section only has to be provided for initial applications, not for post-authorisation procedures.